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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/512,082 02/24/00 NERI

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HM22/1117

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EXAMINER

PORTNER, V

ART UNIT	PAPER NUMBER
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1645

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DATE MAILED:

11/17/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No. 09/512,082	Applicant(s) Neri
Examiner Portner	Group Art Unit 1645

Responsive to communication(s) filed on Sep 18, 2000

This action is FINAL.

Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

- Claim(s) 14-17 and 19-35 is/are pending in the application.
- Of the above, claim(s) 14-17 and 35 is/are withdrawn from consideration.
- Claim(s) _____ is/are allowed.
- Claim(s) 19-34 is/are rejected.
- Claim(s) _____ is/are objected to.
- Claims 14-17 and 19-35 are subject to restriction or election requirement.

Application Papers

- See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- The drawing(s) filed on _____ is/are objected to by the Examiner.
- The proposed drawing correction, filed on _____ is approved disapproved.
- The specification is objected to by the Examiner.
- The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- All Some* None of the CERTIFIED copies of the priority documents have been received.
- received in Application No. (Series Code/Serial Number) _____.
- received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

- Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- Notice of References Cited, PTO-892
- Information Disclosure Statement(s), PTO-1449, Paper No(s). 4
- Interview Summary, PTO-413
- Notice of Draftsperson's Patent Drawing Review, PTO-948
- Notice of Informal Patent Application, PTO-152

-- SEE OFFICE ACTION ON THE FOLLOWING PAGES --

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DETAILED ACTION

Claims 1-13 and 18 have been canceled.

Claims 14-17, 19-35 are pending.

Claims 19-34 are under consideration.

Election/Restriction

1. Applicant's election with traverse of Group IV in Paper No. 3, dated September 1, 2000 is acknowledged. The traversal is on the ground(s) that subject matter presented in the claims is related to all other claims in the application. The traversal was found convincing in part and Groups III and IV will be rejoined. Traversal with respect to the other non-elected Groups I, II and V is not found persuasive for the reasons below.

First, the classification system has no statutory recognition whether inventions are independent and distinct. For example, each class and subclass is comprised of numerous completely independent and distinct inventions.

Second, MPEP 803 states that restriction is proper between patentably distinct inventions where the inventions are (1) independent or distinct as claimed and (2) a serious search and examination burden is placed on the examiner if restriction is not required.

The term "distinct" is defined to mean that two or more subjects as disclosed are related, for example, as product and method of use, but are capable of separate manufacture, use or sale as claimed, and are patentable over each other (see MPEP 802.1). In the instant situation, the

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inventions of Groups II and V (Group I claims have been canceled) are drawn to distinct inventions which are related as separate products capable of separate functions. Restrictions between the inventions is deemed to be proper for the reason previously set forth.

In regard to burden of search and examination, MPEP 803 states that a burden can be shown if the examiner shows either separate classification, different field of search or separate status in the art. In the instant case a burden has been established in showing that the inventions of Groups I-V are classified separately necessitating different searches of issued US Patents. However, classification of subject matter is merely one indication of the burdensome nature of search. The literature search, particularly relevant in this art, is not co-extensive, because for example in vitro and in vivo use of antibodies clearly define different areas of biomedical endeavor. Additionally, it is submitted that the inventions of Groups I-V have acquired a separate status in the art. Clearly different searches and issues are involved in the examination of each Group.

For these reasons the restriction requirement is deemed to be proper and is therefore made

Final.

2. Claims 14-17 and 35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected Groups II and V there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 3 dated September 1, 2000.

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5/25/15/00
Information Disclosure Statement

The information disclosure statement filed September 18, 2000 has been considered.

Specification

4. The disclosure is objected to because of the following informalities: The instant specification recites a hyperlink to the Internet. This is not permitted in Official Patent Applications (Form paragraph 7-29-04) Appropriate correction is required.

- Sequence Letter* *Compliance, confusing @ P 817, clarification SEQ next to sequence*
5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821 (a) (1) and (a) (2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

6. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.136. In no case may an applicant extend the period of response beyond the six month statutory period and the response period is the time set in this action. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

7. Specifically:

- a. see page 19, lines 26-27, where a total of four sequences are described, 2 amino acid and 2 nucleic acid sequences. Only two SEQ ID Nos. assigned to these two sequences. Also, one of the amino acid sequences is confusing because it appears on two different lines. All

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amino acid sequences of 4 amino acids in length or more and any nucleic acid sequence of 9 nucleotides or more need to be assigned a SEQ ID NO.

b. Figure 6 refers to only a single SEQ ID NO, the figure should define the three sequences shown and therefore should be assigned 3 SEQ ID NOS,

Specification

Content of Specification

8. Brief Description of the Several Views of the Drawing(s): A reference to and brief description of the drawing(s) as set forth in 37 CFR 1.74. Drawings. See 37 CFR 1.81, 1.83-1.85, and MPEP § 608.02.
9. The Brief Description of the Drawings and the figures shown do not evidence clear labels and description of the contents of the figures.
 - a. Figure 1A & 1B should be recited and briefly described.
 - b. Figure 2A & 2B should be recited and briefly described.
 - c. Figure 3 A,B &C should be recited and briefly described.
 - d. Figure 4 A,B &C should be recited and briefly described
 - e. Figure 6 refers to only a single SEQ ID NO, the figure should define the three sequences shown and therefore should be assigned 3 SEQ ID NOS,
 - f. Figure 7, each frame (A-H) should be labeled and briefly described. Figure 7 shows several abbreviations. These abbreviations should be defined in the Brief Description of the Drawings. Clarification of the abbreviations is requested.

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- g. Figure 9, each frame (A-C) should be labeled and briefly described.
 - h. Figure 10, each frame (A-D) should be labeled and briefly described.
 - i. Figure 11, each frame (A-L) should be labeled and briefly described.
 - j. Figure 12, each frame (A-L) should be labeled and briefly described.
 - k. Figure 13, each frame (A-B) should be labeled and briefly described.
 - l. Figure 14, each frame (A-C) should be labeled and briefly described.
 - m. Figure 15, each frame (A-B) should be labeled and briefly described.

Claim Rejections - 35 U.S.C. § 101

10. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

11. Claims 19 and 29-34 provide for the use of an antibody, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

12. Claims 19 and 29-34 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for

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example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

JK
a. Claim 19 recites a “wherein” statement. This ~~is~~ ^{does} not define a positive method~~s~~ step. It is a descriptive phrase. The last phrase of the claim recites “is used”. Therefore the claim is a “Use” claim. Amendment of the claim to recite positive methods steps could obviate this rejection.

JK
b. Claims 29-34 recite descriptive “wherein” phrases defining a “Use” for a conjugate.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 19, 20-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

OIC
a. Claim 19 recites at least two different methods, specifically “diagnosis” and “therapy of tumors and diseases”. These methods are very different and would require different methods steps to accomplish the intended purpose of the method. The claim therefore does not distinctly claim Applicant’s invention.

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b. Claim 19 recites the phrase "characterized by" and "characteristic epitope", what these phrases mean is not distinctly claimed. Amendment of the claim to recite the word --comprising-- in place of the phrase "characterized by" could partially obviate this rejection.

14. Claims 20-34 ~~are~~ depend from canceled claim 1 and are therefore vague and indefinite.

i. If the claims were amended to include the claim limitations recited in **claim 1**, they would recite the phrase "improved affinity to said ED-B epitope". A point of reference for antibody binding has not been defined in the claims. Therefore, how the affinity is improved is not distinctly claimed. The term "improved" in claim 1 is a relative term which renders the claim indefinite. The term "improved" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The recitation of this phrase in the claim would not distinctly claim Applicant's invention.

ii. The phrase "said ED-B epitope" recited on line 3 of **claim 1** lacks antecedent basis in claim 1, line 1 which recites the word "domain". No specific epitope is defined, any epitope that is characteristic of the ED-B is recited in line one of the claim. What defines a characteristic epitope is not distinctly claimed.

iii. Claim 1 recites the abbreviation ED-B. Abbreviations must be defined at their first appearing in the claims in order for the claimed invention to be clear. Clarification is requested.

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15. Claim 31 does not further limit the method of claim 30, but defines a different disease.

What method step is further recited in defining a different disease is not distinctly claimed.

Clarification of the claimed method step(s) is requested. It is not clear what other pathologies are being treated in the method if the "angiogenesis-related pathology" is only "associated with ocular angiogenesis". What this ~~associated~~ is not distinctly claimed.

16. Claim 34 depends from claim 28, which recites the phrase "is represented by a photosensitizer and a radio nucleotide". What the representation defines in the composition is not clear. If the phrase "is represented" intends to define open language, the claim could be made ~~clearer~~ clearly through amendment to recite the word --comprising-- and deletion of this phrase.

17. Claims 19, and 29-34 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: providing a conjugate, a subject to whom the reagent is administered and a correlation step with the preamble of the claim.

Claim Rejections - 35 U.S.C. § 102

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

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(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

Please Note: The following art rejection being made over the methods claims are being made in light of the best possible reading of the claims with specific active voice method steps being recited.

19. Claim 19 is rejected under 35 U.S.C. 102(b) as being anticipated by CFRnemolla et al (1996, reference provided in Applicant's 1449).

Monoclonal antibodies were used in an immunoassay (ELISA) method and tissue staining assays for the presence of fibronectin ED-B domain in tumor tissue (see abstract, second to last line "neoplastic tissues").

Carnemolla et al disclose recombinant humanized polypeptide antibodies, specifically scFv antibodies, that specifically bind to Fibronectin ED-B domain and specifically bind to ED-B with an affinity of 53 nM and 1.1 nM (see results, col. 1, page 400, paragraph 3).

Immunoreactivity was specific for Fibronectin type III repeat sequences of about 40 kilodaltons and 45 kilodaltons (see Figure 1, page 398, top of page) and with human fibronectin subunit fragments of about 85 and 120 kilodaltons (see page 399, Figure 2).

The reference anticipates the now claimed invention.

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20. Claims 19, 20-23, 25, 29-31 are rejected under 35 U.S.C. 102(b) as being anticipated by Neri et al (WO97/45544, reference provided in Applicant's 1449).

(Conjugate claims 20-23, 25) Neri et al disclose recombinant polypeptide antibodies, specifically scFv antibodies, that specifically bind to Fibronectin ED-B domain with high affinity (see claims 14, 16, and 22-23). Dimeric scFv antibodies are known to evidence the capability of inducing occlusion and are claimed at claim 16 of the WO97 document. (see Neri, Nature Biotechnology, November 1997, page 1271, col. 1, third paragraph, last 2 lines; reference of record in Applicant's 1449)

Conjugates that comprised scFv fragments together with a FLAG tag or with biotin were also disclosed (see page 37, line 20; see page 38, line 12-19).

Labeled antibody with a photosensitizer that absorbs above 600 nm was made (see page 35, lines 30-37; page 36, lines 1-37). The label was described as producing fluorescence, absorption at 747 nm, obtained from Amersham label Cy-7-bis-OSu.

Antibodies conjugated with a propidium iodine label, or a radio nucleotide label: I¹²⁵, In¹¹¹ and ^{99m}TC (see page 16, lines 1-12) are specifically taught.

The antibodies are taught for use in vivo and in vitro, and may be radio labeled with radioactive iodine (see page 16, lines 6-7). The antibodies bind to an epitope of ED-B domain. Limited changes to the CDRs are claimed (see 10-13) for the specific antibodies disclosed. The

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reagents are claimed in kit form and would therefore comprise an antibody and the needed reagents to conduct the assay (see claim 29).

(Method Claims 19, 29-31) One of the above described conjugates was administered in vivo (mice, see page 36, lines 12-18) and imaged using an infrared mouse imager (a type of irradiation, see page 36, line 19). Injected conjugates detected the presence of tumor cells visualized at a macroscopic level (see page 38, line 29; page 37, lines 11-13) and also resulted in tumor clearance (treatment).

The reference anticipates the now claimed conjugates and methods.

21. Claims 19, 20, 25, 29, 32 are rejected under 35 U.S.C. 102(a) as being anticipated by Mariani et al (December 15, 1997).

The reference discloses a radio labeled monoclonal antibody that specifically binds to Fibronectin extra domain B+ that recognizes the human isoform present in the oncofetal domain. The antibody was used in vivo to visualize malignant brain tumor tissue growth. The radio labeled antibody was useful in diagnosis, specifically for immunoscintigraphy in cancer patients.

Inherently the disclosed antibody anticipates the now claimed invention.

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22. Claim 20 is rejected under 35 U.S.C. 102(e) as being anticipated by Thorpe et al (US Pat. 6,093,399).

Thorpe et al claim a composition that comprises an antibody to a tumor associated fibronectin isoform, and specifically discloses the use of monoclonal antibody BC-1 that is specific for the ED-B domain of fibronectin (see Tables IV and V). The reference teaches preferred targetable elements of tumor-associated stroma are currently the tumor-associated fibronectin isoforms. Fibronectin isoforms are ligands that bind to the integrin family of receptors. Tumor-associated fibronectin isoforms are available, e.g., as recognized by the MAb BC-1. This Mab, and others of similar specificity, are therefore preferred agents for use in the present invention. Fibronectin isoforms, although stromal components, bind to endothelial cells and may thus be considered as a targetable vascular endothelial cell-bound ligand in the context of the invention.

Formulation of a bi-specific antibody following the guidance provided results in a binding agent that has coagulant activity. A coagulant is a reagent that is specific for induction of in vivo coagulation of tumor vasculature, causing tumor regression, through the site-specific delivery. Assessment of binding for any of the disclosed bispecific antibodies is taught through the assay of a radio labeled coagulant to a target cell via bridging with the bispecific ligand or antibody. Such an assay is exemplified by the binding of tTF to target cells using the B21-2/10H10 bispecific antibody, as described in Example II

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The reference claims a conjugate bispecific reagent that comprises an antibody that binds to a tumor associated fibronectin isoform linked to a coagulation factor (see claims 1, 17-18 and 47).

Inherently the reference discloses the now claimed invention.

23. Claims 20 and 29 are rejected under 35 U.S.C. 102(e) as being anticipated by Thorpe et al (US Pat. 6,093,399).

Thorpe et al claim a method of treating cancer through the administration of a composition that comprises an antibody to a tumor associated fibronectin isoform, and specifically discloses the use of monoclonal antibody BC-1 that is specific for the ED-B domain of fibronectin (see Tables IV and V) linked to a second binding agent that results in coagulation in the vasculature of the tumor (see claims 21, 22, 29, 41-42 and 49-50).

Inherently the reference discloses the now claimed conjugate and method of using said conjugate.

Claim Rejections - 35 U.S.C. § 103

24. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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25. Claims 26 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Neri et al (WO97/45544) as applied to Claims 19, 20-23, 25, 29-30 above, in view of Goldenberg (US Pat. 5,776,095; filing date June 1, 1995).

See discussion of Neri above. The reference teaches conjugates of an antibody with a radionucleotide but differs from the instantly claimed invention by failing to show the use of alpha and beta emitters, specifically the use of astatine-211 or bismuth-212.

Goldenberg shows the use of antibody conjugates (see col. 9, lines 8-64; especially lines 36-37) that comprise alpha and beta emitters in an analogous art for the purpose of producing conjugates useful in cancer therapy.

In view of the prior art teaching that alpha and beta radionucleotides are effective in the formulation of conjugates for clinical applications, wherein the emitters are astatine or bismuth radionucleotides, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the conjugate of Neri that comprises a radio nucleotide gamma emitter, with the alpha or beta emitter of Goldenberg because Astatine-211 and Bismuth-212 provide means for localization and therapy of abnormal tissues and evidence a longer half life than that of a gamma emitter, thus providing for a longer half life, localized at the site of the abnormal tissue and are also known to cause reduced genetic damage as compared to gamma emitter radionucleotides.

Therefore, in the absence of a showing of unexpected results, the person of ordinary skill in the art would have been motivated to select an alpha or beta emitter in the place of a gamma

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emitter radio nucleotide because of the realized advantages of increased half life and the likelihood of reduced random genetic damage to normal tissues in the vicinity of the abnormal tissue to which the conjugate would bind.

26. Claims 24 ¹⁵ rejected under 35 U.S.C. 103(a) as being unpatentable over Neri et al as applied to claims 19, 20-23, 25, 29-30 above ^{and further} in view of Fritzberg et al (US Pat. 5,976,535; filing date June 1995)

See discussion of Neri above. The reference teaches conjugates of an antibody with a photosensitizer but differs from the instantly claimed invention by failing to show the use ^{of} tin(IV) choline e6.

Fritzberg et al teach the use of antibody conjugates that comprise tin(IV) choline e6 (col. 28, line 2) photosensitizer in an analogous art for the purpose of producing conjugates useful in photodynamic therapy that are readily incorporated into the conjugate molecule (see col. 27, lines 16-24). Photosensitizer molecules are taught to have ^a ^{long half} ^{life}, generally up to two months (see col. 28, lines 24-25), evidence a strong absorption band between 600 and 700 nm and provide a means for enhanced performance of photodynamic therapy protocols (see col. 27, lines 58-63).

In view of the prior art teaching that photosensitizers are effective in the formulation of conjugates for clinical photodynamic therapy, wherein the photosensitizer is tin(IV)choline e6, it would have been obvious to the person of ordinary skill in the art at the time the invention was

made to modify the conjugate of Neri that comprises a photosensitizer, with the photosensitizer of Fritzberg because Fritzberg et al teach means and methods of utilizing photosensitizer that facilitate target cell specific accretion of photosensitizing agent and obviate the necessity for a recipient to avoid direct sunlight (see col. 28, lines 30-36).

Therefore, in the absence of a showing of unexpected results, the person of ordinary skill in the art would have been motivated to select the tin chlorin e6 photosensitizer of Fritzberg in the place of photosensitizer of Neri because of the realized advantage that the recipient of the conjugate that comprises the photosensitizer need not avoid direct sunlight and may even obtain a residual benefit from exposure to sunlight which is unlike other previously known photosensitizers (see Fritzberg, col. 28, lines 30-36).

27. Claims 26, 27 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mariani et al (December 15, 1997) as applied to Claims 19, 20, 25, 29, 32 above, ^{and further} in view of Goldberg (US Pat. 5,776,095; filing date June 1, 1995).

See discussion of Mariani et al above. The reference teaches conjugates of an antibody with a radio nucleotide but differs from the instantly claimed invention by failing to show the use of alpha and beta emitters, specifically the use of astatine-211 or bismuth-212.

Goldenberg shows the use of antibody conjugates (see col. 9, lines 8-64; especially lines 36-37) that comprise alpha and beta emitters in an analogous art for the purpose of producing conjugates useful in cancer therapy.

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In view of the prior art teaching that alpha and beta radionucleotides are effective in the formulation of conjugates for clinical applications, wherein the emitters are astatine or bismuth radionucleotides, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the conjugate of Mariani et al that comprises a radio nucleotide gamma emitter, with the alpha or beta emitter of Goldenberg because Astatine-211 and Bismuth-212 provide means for localization and therapy of abnormal tissues and evidence a longer half life than that of a gamma emitter, thus providing for a longer half life period of time localized at the site of the abnormal tissue and are also known not to cause reduced genetic damage as compared to gamma emitter radionucleotides.

Therefore, in the absence of a showing of unexpected results, the person of ordinary skill in the art would have been motivated to select an alpha or beta emitter in the place of a gamma emitter radio nucleotide because of the realized advantages of increased half life and the likelihood of reduced random genetic damage to normal tissues in the vicinity of the abnormal tissue to which the conjugate would bind.

Conclusion

28. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.
29. Reed (US Pat. 5,746,997) is cited to show benzoic acid labels.

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30. Slepian et al (US Pat. 5,843,156) is cited to show a local polymeric gel cellular therapy that comprises components that interface with fibronectin (see Example 5, col. 18-21).

31. Thorpe et al (US Pat. 6,036,955) is cited to show kits that comprise bispecific reagents for induction of coagulation.

This is a non-final action.

No claims are allowed.

32. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for this group is (703) 308-4242.

The Group and/or Art Unit location of your application in the PTO will be Group Art Unit 1645. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to this Art Unit.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.
Vgp

November 15, 2000

LFS
LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Notice to Comply	Application N .	Applicant(s)
	09/512,082 Examiner Portner	Neri Art Unit 1645

**NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS
CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE
DISCLOSURES**

Applicant must file the items indicated below within the time period set by the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).
- 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked-up "Raw Sequence Listing."
- 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

- 7. Other:

Applicant Must Provide:

- An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216

For CRF Submission Help, call (703) 308-4212

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